Respiratory Medicine (2003) **97**, 1134–1142

ELSEVIER

respiratoryMEDICINE

Sequential IV/PO moxifloxacin treatment of patients with severe community-acquired pneumonia ☆

H. Lode[a,*], C. Grossman[b], S. Choudhri[c], D. Haverstock[c], J. McGivern[d], Z. Herman-Gnjidic[e], D. Church[c]

[a]*Zentralklinik Emil von Behring, Lungenklinik Heckeshorn, Berlin 10115, Germany*
[b]*Palmetto Internal Medicine, Summerville, SC 29485, USA*
[c]*Bayer Corp, West Haven, CT 06516, USA*
[d]*Bayer plc, Strawberry Hill, Newbury, Berkshire RG14 1JA, UK*
[e]*Bayer Inc., 77 Belfield Road, Toronto, Ont., Canada M9W1G6*

KEYWORDS
Moxifloxacin;
Severe pneumonia;
Amoxicillin clavulanate;
Clarithromycin;
Levofloxacin;
Trovafloxacin

Summary *Background*: IV/PO moxifloxacin was evaluated in the treatment of hospitalized patients with severe community-acquired pneumonia (CAP).

Methods: Data were pooled from two prospective, randomized studies. In the multinational study, patients received 7–14 days IV/PO moxifloxacin 400 mg QD or IV/PO amoxicillin clavulanate 1200/625 mg TID ± IV/PO clarithromycin 500 mg BID. In the North American study, patients received 7–14 days IV/PO moxifloxacin 400 mg QD, IV/PO alatrofloxacin/trovafloxacin 200 mg QD, or IV/PO levofloxacin 500 mg QD. The primary endpoint was clinical success at the test-to-cure visit. Severe CAP was defined according to the 1993 ATS criteria.

Results: In the clinically valid population, clinical success rates were 88% (167/190) for moxifloxacin- and 83% (155/186) for comparator-treated patients (95% CI = −1.9%, 12.2%). Corresponding clinical success rates for the microbiologically valid population were 87% (59/68) and 84% (54/64), respectively (95% CI = −8.6%, 15.0%). A switch from IV to PO therapy was made by day 5 of therapy for 73% of moxifloxacin- vs. 60% of comparator-treated patients ($P < 0.01$). Clinical success rates were similar in a retrospective analysis using the revised 2001 ATS definition of severe CAP. Mortality rates were 6% (15/241) and 10% (24/238) in the moxifloxacin and comparator treatment groups, respectively. The incidence of drug-related adverse events was similar in both treatment groups.

Conclusion: Sequential IV/PO moxifloxacin 400 mg QD is as safe and effective as other fluoroquinolones and a β-lactam/macrolide combination for treating hospitalized patients with severe CAP.

Introduction

Community-acquired pneumonia (CAP) remains a prevalent and potentially life-threatening infection, with the US reporting almost 4 million new cases and the UK diagnosing at least 250,000 adults each year.[1,2] Approximately 25–35% of new cases

☆This work was supported by a research grant from Bayer Corporation, Pharmaceutical Division, West Haven, Connecticut.
*Corresponding author: Department of Chest and Infectious Diseases, Chest Hospital Zehlendorf/Heckeshorn, Central Clinic Emil von Behring, Zum Heckeshorn 33, 14109 D-Berlin, Germany. Tel.: +49-30-800-222-23; fax: +49-30-800-226-23.
E-mail address: haloheck@zedat.fu-berlin.de (H. Lode).

0954-6111/03/$ - see front matter
doi:10.1016/S0954-6111(03)00166-5

require hospitalization,[1,2] and for critically ill patients with CAP, mortality rates range from 5% to as high as 30–50%[1,3–5]. Indeed, pneumonia is the leading cause of infection-related mortality and is responsible for an estimated 45,000 deaths per year in the US.[1]

In general, CAP is considered severe when hospitalization is required, and this often suggests a poorer prognosis. Severe CAP in patients of any age is usually characterized by one or more of the following criteria: acute respiratory failure, hemodynamic compromise, severe sepsis and septic shock, multilobar radiographic infiltrates, plus some additional laboratory parameters (e.g., blood urea nitrogen >7 mM, lactate dehydrogenase >260 U/l and low serum albumin at admission).[6–8] Although there is no uniform objective definition for severe CAP, patients with any of these characteristics require hospitalization and prompt antimicrobial treatment.[1,7,9]

Determining the etiology of CAP remains challenging, with no pathogenic organism(s) being identified in up to 50% of patients. Despite the limitations of current diagnostic tests, a concerted effort should be made to identify the causative organism in patients with severe CAP as this may confirm the appropriateness of the empiric antimicrobial therapy.[1,7] *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, aerobic Gram-negative bacilli, *Legionella* spp., *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* are the most frequently isolated pathogens from patients of any age who require hospitalization for CAP.[1,7,10] The empiric antimicrobial regimen must be highly effective against *S. pneumoniae* as this organism has been identified as the etiologic pathogen in nearly two-thirds of patients who have died of pneumonia,[11] and is the most commonly isolated pathogen from the elderly and patients with underlying medical conditions.[1,7]

Treatment of severe CAP is challenging and is influenced by an extensive list of possible pathogens, new antimicrobial options, and emergence of resistance to some antimicrobials especially against *S. pneumoniae*.[12–16] For hospitalized patients who do not require admission to the intensive care unit (ICU), the most recent guidelines published by the Infectious Diseases Society of America (IDSA) recommend monotherapy with a newer fluoroquinolone or the combination of an extended-spectrum cephalosporin plus a macrolide.[1] For the most severe CAP episodes (i.e., those requiring ICU admission), the IDSA has recommended the combination of a β-lactam (e.g., ceftriaxone, ampicillin sulbactam) with either a macrolide or fluoroquinolone.[1] Similar recommendations are found in the most recent American Thoracic Society (ATS) [7] and British Thoracic Society (BTS) guidelines.[17] Following initial improvement, some patients with severe CAP may be candidates for sequential IV to oral therapy.[1,7,18–22]

Moxifloxacin (Avelox; Bayer AG: Wuppertal, Germany), a new 8-methoxy quinolone, has excellent and potent in vitro activity against both typical Gram-negative and Gram-positive aerobes and atypical pathogens commonly associated with severe CAP.[23,24] Further, moxifloxacin remains active against penicillin-resistant *S. pneumoniae*[23,24] Moxifloxacin's pharmacokinetic/pharmacodynamic profile permits once daily dosing and bioequivalence of oral and IV formulations allows for convenient sequential IV to PO therapy without dosage adjustment.[25] The aim of this pooled analysis was to evaluate the efficacy and safety of sequential (IV/PO) moxifloxacin compared with standard IV/PO antimicrobials (i.e., other fluoroquinolones or a β-lactam/macrolide combination) in the treatment of patients hospitalized with severe CAP, including those considered to be critically ill.

Patient population and methods

Patient selection

In this retrospective study of patients with severe CAP, data were pooled from two prospective, randomized clinical trials with moxifloxacin: one multinational study was conducted in Europe, Israel and South Africa; the other study was conducted in North America. The patient eligibility criteria for both the multinational and North American studies were similar and included: age $\geqslant 18$ years with signs and symptoms consistent with bacterial pneumonia (mild to moderately severe CAP and severe CAP) requiring IV therapy. CAP was documented by the presence of fever and/or elevated WBC count ($>10{,}000/mm^3$), WBC count $\leqslant 4500/mm^3$, or $\geqslant 15\%$ immature neutrophils plus a new or progressive infiltrate on chest X-ray confirmed by a radiologist. In addition, each patient had to have at least one sign or symptom of pneumonia (i.e., productive cough, purulent sputum, dyspnea or tachypnea (>20 breaths/min), rigors/chills, pleuritic chest pain, or signs of pulmonary consolidation). For the purposes of this retrospective analyses, only patients classified as having severe CAP (see below) were included.

Both trials excluded patients who resided in a nursing home and those hospitalized for >48 h

before the onset of pneumonia symptoms. Patients were also excluded if they had a history of any of the following: bronchial obstruction or post-obstructive pneumonia; suspected aspiration pneumonia or pulmonary tuberculosis; prior therapy with a systemic antibiotic for >24 h prior to enrollment (unless a failure with identification of a pathogen); moderate to severe liver (Child-Pugh B/C) or renal (Cl_{Cr} <50 ml/min) impairment; prolonged QT_c interval; using Class IA or III antiarrhythmics; uncorrected hypokalemia; absolute neutrophil count <1000 cell/mm^3 or significant immunosuppression; and rapidly fatal underlying disease.

Each patient provided written informed consent following approval of the protocol by each institution's internal review board and in accordance with the Declaration of Helsinki.

Definition of severe CAP

In both the multinational and North American studies, severe pneumonia was defined according to the 1993 ATS criteria and included the presence of at least one of the following conditions: respiratory rate >30 breaths/min pretherapy, PaO_2/FIO_2 ratio <250 mmHg or $PO_2 \leqslant 8$ kPa (60 mmHg); requirement for mechanical ventilation; chest radiograph indicating bilateral or multilobe involvement; increase in the size of opacity by $\geqslant 50\%$ within 48 h of admission; shock (systolic blood pressure <90 mmHg or diastolic pressure <60 mmHg); requirement for vasopressor therapy for >4 h; and urine output <20 ml/h or a total urine output <80 ml/h unless another explanation was provided.[26]

Following completion of the multinational and North American trials, new ATS guidelines were published in 2001.[7] The latest guidelines define severe CAP as the presence of either one of two major criteria (need for mechanical ventilation or septic shock) or the presence of two of three minor criteria (systolic blood pressure $\leqslant 90$ mmHg, multilobar disease, and PaO_2/FIO_2 ratio $<$ 250 mmHg).[7]

Study design and antimicrobial therapy

Each study in this pooled analysis was a prospective, multi-center, Phase III clinical trial. The North American study was double-blinded, while the multinational investigation had an open-label design. Patients categorized with CAP were randomized to receive either moxifloxacin (Avelox, Bayer AG, Wuppertal, Germany), or a comparator antibiotic using a block random code that was computer-generated.

In the multinational trial, patients were randomized to either moxifloxacin or amoxicillin clavulanate (Augmentin, SmithKline Beecham, Philadelphia, PA). The following regimens were administered: IV/PO moxifloxacin 400 mg QD or IV/PO amoxicillin clavulanate 1200/625 mg TID $\pm$ IV/PO clarithromycin 500 mg BID (Biaxin, Abbott Laboratories, Chicago, IL).

In the North American trial, patients were randomized to either IV/PO moxifloxacin QD (Avelox, Bayer Corporation Pharmaceutical Division, West Haven, CT) or IV/PO alatrofloxacin/trovafloxacin 200 mg QD (Trovan I.V./Trovan tablets, Pfizer, Roerig, New York, NY). Following concerns about trovafloxacin-related hepatotoxicity in late 1999, subsequently enrolled patients were randomized to receive either moxifloxacin, or IV/PO Levofloxacin 500 mg QD (Levaquin, Ortho Pharmaceutical Corporation, Raritan, NJ). A "double-dummy" approach was used to maintain the blinding.

In both trials, patients were to receive IV antibiotic (each as 60 min infusion) for at least 3 days. Each patient was to receive a total of 7–14 days of IV/PO therapy. The switch to the assigned oral antibiotic was based on criteria previously reported and included:[27]

- clinical response (resolution of fever, improved cough and respiratory distress, improvement in leukocytosis);
- chest radiographs (if deemed clinically necessary) to determine if the condition was improving, unchanged or worsening;
- ability to tolerate oral therapy;
- no evidence of markedly decreased gastrointestinal motility or malabsorption; and
- the investigator's judgement.

Efficacy and safety measurements

The effectiveness of the study drug was determined by assessing the patients' clinical response, as well as the presumed or documented bacteriologic response of the infecting organism. Microorganisms were primarily isolated from sputum or blood.

The clinically valid population included patients who satisfied the following criteria: (1) had no protocol violations influencing efficacy; (2) had radiologic evidence of new or progressive infiltrate consistent with pneumonia; (3) received at least 48 h of antimicrobial therapy if a treatment failure or at least 5 full days of therapy if a treatment success; and (4) took no other antimicrobial agent

with the study drug for the entire study period unless they were a treatment failure. Clinical response at the test-of-cure visit (5–7 days for multinational trial vs. 7–30 days post-therapy for the North American trial) was defined as Cure (disappearance of acute signs and symptoms related to the infection or sufficient improvement such that additional or alternative antimicrobial therapy was not required), Failure (insufficient lessening of the signs and symptoms of infection such that additional or alternative antimicrobial therapy was required), or Indeterminate (a clinical assessment was not possible for any reason).

Bacteriological responses were graded as eradication, presumed eradication (if no material was available due to a clinical success), persistence, presumed persistence (no material was available in a patient considered a clinical failure), or indeterminate (if bacteriological response to the study drug was not evaluable for any reason).

All patients receiving at least one dose of study drug were evaluated for drug safety (intent-to-treat population). Safety of study drug therapy was monitored by clinical observations and by conventional laboratory tests. Adverse events were rated by the investigator as to their severity (mild, moderate, severe), and by the relationship to the study drug (probable, possible, remote, or none).

Statistical analyses

Demographic and baseline characteristics were pooled for the two studies and summarized for each treatment group (i.e., moxifloxacin vs. comparator). These summaries included means, standard deviations, medians, and quartiles for continuous data and frequency counts for categorical variables.

Two-sided 95% confidence interval (CI) were constructed around the mean clinical success rates using Mantel–Haenszel weights, using the sample size of the respective studies as the weights. Similar analyses were performed for the population considered to be microbiologically valid and for the intent-to-treat population (i.e., all patients who received at least one dose of study drug). Clinical success rates were calculated using the protocol-derived definition of severe CAP. An exploratory, retrospective analysis of the clinical success rates was also performed using the new 2001 ATS definition for severe CAP.

Comparison of the incidence of adverse events in each treatment group was done in a descriptive manner. Safety analyses included tabulations of type (COSTART), frequency, duration, and drug-relatedness of treatment-emergent events.

Results

The pooled analysis included a total of 479 severe CAP patients who were randomized to receive a study antibiotic in the two trials. Two hundred and forty-one patients received moxifloxacin, and 238 patients received a comparator antimicrobial. A total of 376 patients (190 moxifloxacin, 186 comparator) satisfied the a priori definition of being clinically valid. A respiratory pathogen was isolated pretherapy in 68 moxifloxacin- and 64 comparator-treated patients (microbiologically valid population).

The demographics and baseline medical characteristics of the intent-to-treat and clinically valid populations suggest that the two treatment groups were similar (Table 1). In general, patients with severe CAP were male ($>60\%$) and Caucasian ($>75\%$). The mean age was 57 years. The reason most cited for severe CAP was bilateral or multilobar pneumonia (49%). More than a third of patients categorized with severe CAP had a respiratory rate >30 bpm and/or a PaO_2/FIO_2 ratio <250 mmHg. Slightly more patients randomized to moxifloxacin were in shock (30%) compared with those given the comparator antimicrobial (24%). Few patients required mechanical ventilation ($\leqslant 2\%$).

Pretherapy pathogens

A total of 186 of 479 (39%) patients defined as intent-to-treat had 252 potential pathogens identified pretherapy from the respiratory tract or blood. Specifically, 97 moxifloxacin-treated patients had 129 pathogens and 89 comparator-treated patients had 123 pathogens identified at baseline. The following pathogens were most commonly identified from the respiratory tract: *S. pneumoniae* (38 moxifloxacin, 38 comparator), *H. influenzae* (21 moxifloxacin, 15 comparator), *M. pneumoniae* (11 moxifloxacin, 10 comparator), *C. pneumoniae* (three moxifloxacin, six comparator), *Legionella* spp. (one moxifloxacin, three comparator), and *S. aureus* (eight moxifloxacin, seven comparator). Of 34 patients with an atypical pathogen identified pretherapy, 11 had mixed infection (four moxifloxacin, seven comparator).

A total of five (three moxifloxacin, two comparator) *S. pneumoniae* isolates were penicillin-resistant (PRSP; MIC $\geqslant 2\,\mu g/ml$). In addition, nine (five

Table 1 Demographic and baseline medical characteristics.

	Intent-to-treat population		Clinically valid population	
	Moxifloxacin ($N = 241$)	Comparator ($N = 238$)	Moxifloxacin ($N = 190$)	Comparator ($N = 186$)
Sex, no. (%) male	145 (60)	147 (62)	116 (61)	114 (60)
Race, no. (%) Caucasian	187 (79)	183 (77)	147 (77)	141 (75)
Mean age (years) at enrollment (range)	58 (18–89)	57 (18–93)	58 (18–89)	56 (19–93)
Definition of severe				
No. (%) respiratory rate >30 bpm	98 (41)	95 (40)	78 (41)	73 (39)
No. (%) PaO_2/FIO_2 ratio <250 mmHg	93 (39)	99 (42)	73 (38)	80 (43)
No. (%) requiring mechanical ventilation	4 (2)	3 (1)	4 (2)	1 (<1)
No. (%) with bilateral or multilobar involvement	107 (44)	135 (57)	83 (44)	102 (54)
No. (%) with increases in opacity on chest X-ray by $\geqslant 50\%$ within 48 h of admission	1 ($<1\%$)	1 ($<1\%$)	1 ($<1\%$)	0
No. (%) with shock	72 (30)	57 (24)	58 (31)	43 (23)
Mean duration of infection, days	5	5	5	5

Table 2 Clinical resolution at test of cure in patients with severe CAP.

Population	Moxifloxacin n/N (%)	Comparator n/N (%)
Intent-to-treat population[a]	171/241 (71)	161/238 (68)
Clinically valid population[b]	167/190 (88)	155/186 (83)
Microbiologically valid population[c]	59/68 (87)	54/64 (84)

[a]95% CI $= -4.4\%$, 12.0%.
[b]95% CI $= -1.9\%$, 12.2%.
[c]95% CI $= -8.6\%$, 15.0%.

moxifloxacin, four comparator) *H. influenzae* isolates produced β-lactamase. No *S. aureus* isolates were found to be methicillin-resistant.

A total of 38 ITT patients had confirmed bacteremia including 20 moxifloxacin- and 18 comparator-treated patients. *S. pneumoniae* was the most frequently isolated organism causing bacteremia (14 moxifloxacin, 11 comparator). Other organisms included staphylococcal and streptococcal species (e.g., *S. aureus*, *Staphylococcus epidermidis*, *Streptococcus viridans*), *H. influenzae*, *Bacillus cereus* and *Eschericia coli*. No blood isolates were PRSP.

Clinical response

For the clinically valid population, the mean total length of antibiotic therapy was 12 ± 3 days for both treatment groups. A switch from IV to PO therapy was made by day 5 of therapy for 73% (139/190) of moxifloxacin vs. 60% (112/186) of comparator-treated patients ($P < 0.01$). This significant difference in time of switch from IV to PO therapy was driven predominantly by the superior performance of moxifloxacin compared to the β-lactam/macrolide comparators. Similar durations of therapy and time of IV to PO switch were observed for the intent-to-treat and microbiologically valid populations.

Table 2 displays the clinical response at the test-of-cure visit for the clinically valid, intent-to-treat, and microbiologically valid groups. Under the 1993 ATS definition of severe CAP, for the clinically valid population, clinical cure at the test-of-cure visit was 88% for moxifloxacin compared with 83% for the comparator regimen (95% CI $= -1.9\%$, 12.2%). Clinical success rates for those comprising the ITT and microbiologically valid populations were 71% moxifloxacin vs. 68% comparator (95% CI $= -4.4\%$,

Table 3 Eradication rates of most commonly isolated pretherapy causative organisms.

Organism	Moxifloxacin *n/N* (%)	Comparator *n/N* (%)
Respiratory site		
S. pneumoniae	24/26 (92)	25/29 (86)
H. influenzae	14/16 (88)	7/10 (70)
M. pneumoniae	8/9 (89)	9/9 (100)
C. pneumoniae	3/3 (100)	4/4 (100)
S. aureus	2/3 (67)	2/4 (50)
Blood site		
S. pneumoniae	14/14 (100)	10/11 (91)

12.0%) and 87% moxifloxacin vs. 84% comparator (95% CI = −8.6%, 15.0%), respectively.

In the retrospective analysis using the 2001 ATS definition,[7] 39% (95 moxifloxacin vs. 92 comparator) of the pooled population of 479 patients had severe CAP. For the clinically valid population, 89% of moxifloxacin- vs. 81% of comparator-treated patients were clinical successes at the test-of-cure visit. Clinical response rates for the intent-to-treat group were 74% and 60%, respectively.

All five patients (three moxifloxacin, two comparator) with a pretherapy PRSP isolated from a respiratory source were clinical cures at the test-of-cure visit. Of the nine patients with a pretherapy β-lactamase positive *H. influenzae* isolate, clinical success was achieved in five moxifloxacin- and four comparator-treated patients.

Both treatment regimens were effective in treating patients with bacteremia: 95% (19/20) moxifloxacin- vs. 94% comparator-treated patients (17/18) were clinical successes. Both failures at the test-of-cure visit occurred in patients with *S. pneumoniae* infection (one moxifloxacin, one comparator).

Bacteriologic results

The bacteriological eradication rates for the most commonly identified causative respiratory organisms at the test-of-cure visit differed between the two treatment groups (Table 3). For the three most commonly isolated (non-atypical) respiratory pathogens—*S. pneumoniae*, *H. influenzae*, and *S. aureus*—rates of eradication were somewhat higher amongst those receiving moxifloxacin. All five PRSP isolates (three moxifloxacin, two comparator) were presumed eradications at the test-of-cure visit. All β-lactamase producing *H. influenzae* were eradicated (five moxifloxacin, four comparator). In addition, all four patients (one moxifloxacin, three comparator) infected with *Legionella* spp. achieved bacteriologic eradication.

Among patients with bacteremia, 95% (19/20) of moxifloxacin- and 94% (17/18) of comparator-treated patients had the causative blood isolates eradicated. *S. pneumoniae*, the primary blood isolate, was successfully eradicated/presumed eradicated by both moxifloxacin (100%; 14/14) and comparator antimicrobials (91%; 10/11).

Safety and tolerability

Among 479 patients with severe CAP who received at least one dose of study drug, drug-related adverse events were reported in 116 (48%) moxifloxacin-treated patients and 107 (45%) comparator-treated patients (Table 4). The most common drug-related adverse events experienced by both treatment groups were diarrhea (6%) and abnormal liver function tests (5%). Injection site reactions or phlebitis also occurred at similar rates between the two groups (5% moxifloxacin, 7% comparator).

A total of 8% of moxifloxacin- ($n = 19$) and 5.5% of comparator-treated patients ($n = 13$) had study drug discontinued prior to completion of the full treatment course because of a drug-related adverse event. For moxifloxacin-treated patients, events leading to discontinuation of therapy included abnormal liver function tests ($n = 4$), allergic reactions/rash ($n = 3$), and atrial fibrillation ($n = 2$). For comparator-treated patients, the primary events that resulted in early drug discontinuation included worsening pneumonia ($n = 2$), rash ($n = 2$), and increased liver function tests ($n = 2$).

Fifteen (6%) moxifloxacin- and 24 (10%) comparator-treated patients with severe CAP died during the study period. Nine patients (three moxifloxacin, six comparator) died while still receiving study drug. The majority of deaths in both treatment groups were secondary to progression of the patient's infection, development of nosocomial infection, or to underlying illness. Among the 39 patients who died, five (two

Table 4 Incidence rates of drug-related adverse events occurring in >2% of patients.

Adverse event	Moxifloxacin ($N = 241$) *n* (%)	All comparator ($N = 238$) *n* (%)
Any drug-related event	116 (48)	107 (45)
Injection site reaction/ phlebitis	12 (5)	17 (7)
Headache	5 (2)	3 (1)
Diarrhea	15 (6)	14 (6)
Nausea	8 (3)	8 (3)
Vomiting	5 (2)	7 (3)
Oral moniliasis	5 (2)	6 (3)
Insomnia	5 (2)	2 (<1)
Dizziness	5 (2)	4 (2)
Rash	3 (1)	5 (2)
Atrial fibrillation	5 (2)	0 (0)
LFT abnormalities	11 (5)	12 (5)
GGTP increased	1 (<1)	5 (2)

moxifloxacin, three comparator) had bacteremia, 32 (12 moxifloxacin, 20 comparator) were male, 25 (seven moxifloxacin, 18 comparator) had multilobar infiltrates, and eight (three moxifloxacin, five comparator) were in shock during study therapy.

Discussion

There is relatively little published data that prospectively and rigorously examines initial empiric antimicrobial regimens for the treatment of severe CAP, therefore the findings from this large two-study pooled analysis are noteworthy. This analysis demonstrates that sequential IV/PO moxifloxacin therapy in hospitalized patients with severe CAP is at least as efficacious as sequential IV/PO standard fluoroquinolone therapy or IV/PO β-lactam +/−macrolide combination. These findings were consistently upheld for the three populations analyzed including intent-to-treat, clinically valid, and microbiologically valid subsets. Indeed, in all of patient populations analyzed, there was a general trend toward superiority of moxifloxacin in both clinical response and bacterial eradication. Indeed, in the multinational study, from which a subset of patients with severe pneumonia presented in this study was derived, moxifloxacin was found to be significantly superior to amoxicillin clavulante +/−clarithromycin in time of switch from IV to PO therapy, as well as clinical and bacteriological responses.[28] Overall, our analysis provides support for the recent IDSA and ATS treatment guidelines[1,7] which recommend use of an empiric fluoroquinolone monotherapy with *S. pneumoniae* coverage as one option for patients with severe CAP.

The two studies that comprise this pooled analysis were designed in 1997 and used the original 1993 ATS definition for categorizing patients with severe CAP.[26] However, in an analysis of the pooled data using the revised 2001 ATS criteria, the clinical response rates remained similar between the two treatment groups.

S. pneumoniae, *H. influenzae*, Gram-negative enteric bacteria (especially *K. pneumoniae*), and *S. aureus*, as well as atypical organisms (e.g., *Legionella* spp.) are the pathogens most commonly implicated in severe CAP.[1,7] In accordance with other studies,[1] an etiology for our pooled population with severe CAP was only established in about one-third of clinically valid patients. *S. pneumoniae* was isolated from sputum in more than 40% of severe CAP episodes and in more than 66% of patients with bacteremia. Only five cases of PRSP (penicillin MIC $\geqslant 2\,\mu g/ml$) were identified in our pooled population.

Overall, IV/PO moxifloxacin eradicated the majority of causative organisms, including 100% ($n = 14$) of *S. pneumoniae* isolates cultured from blood. Moxifloxacin also provided excellent efficacy against the commonly isolated intracellular pathogens, *M. pneumoniae* and *C. pneumoniae*, 89% and 100%, respectively. Although the number of patients with resistant organisms in this pooled analysis was small, three moxifloxacin- and two comparator-treated patients infected with PRSP (isolates all from respiratory tract sites) were clinically and bacteriologically cured. All β-lactamase producing *H. influenzae* were eradicated and associated with clinical cure following therapy with moxifloxacin. Collectively, these data provide bacteriologic evidence that moxifloxacin is effective against the most common pathogens implicated in causing severe CAP.

Few deaths attributable to infection were observed in our population of patients with severe CAP. However, of the patients that did succumb, many had conditions/characteristics that have been previously defined as prognostic factors indicative of an increased risk of mortality.[11] Such factors included bacteremia, shock, multilobar infiltrates on chest X-ray, and male gender. As such, the group who died was not that unexpected.

The two clinical studies pooled in this retrospective analysis were different in design—one

double blind, the other open label. However, the eligibility criteria, the criteria used to classify patients as having severe pneumonia and the criteria used to evaluate the patients with respect to clinical response were identical. As such, the two trials enrolled very similar patient populations and the patients were assessed in the same way. Additionally, the objective clinical end-points (vital signs, findings on physical exam, radiological findings, etc.) minimized the risk of biased when evaluating patients in the open-label study.

Approximately 10% of hospitalized patients with CAP are categorized as having severe pneumonia. In patients receiving such a diagnosis, mortality rates are high and may exceed 30%, especially in the elderly.[1,3–5] Early recognition of severe CAP and the prompt initiation of broad-spectrum empiric therapy is, therefore, advocated to reduce the risk of mortality.[1,7] The most current IDSA and ATS CAP guidelines recommend the use of fluoroquinolone monotherapy as one option for hospitalized patients with severe CAP.[1,7] Results from our pooled analysis provide clinical and bacteriologic evidence that a sequential IV/PO moxifloxacin regimen is at least as effective as the comparator fluoroquinolones and a β-lactam/β-lactamase inhibitor plus macrolide combination in the treatment of severe CAP. Treatment with IV/PO moxifloxacin was associated with a low mortality rate and few untoward adverse reactions.

Acknowledgements

The authors acknowledge all the investigators who participated in the multinational and North American studies. We also thank Brian Shearer, Ph.D. and Teresa Tartaglione, PharmD for editorial contributions.

References

1. Bartlett JG, Dowell SF, Mandell LA, et al. Practice guidelines for the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2000;**31**:347–82.
2. Guest JF, Morris A. Community acquired pneumonia: the annual cost to the national health service in the UK. *Eur Respir J* 1997;**10**:1530–4.
3. Centers for Disease Control and Prevention. Premature deaths, monthly mortality and monthly physician contacts–United States. Morb Mortal Wkly Rep 1997; 46: 556.
4. Pinner RW, Teutsch SM, Simonsen L, et al. Trends in infectious diseases mortality in the United States. *JAMA* 1995;**275**:189–93.
5. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997;**335**:243–50.
6. Ewig S, Schäfer H, Torres A. Severity assessment in community-acquired pneumonia. *Eur Respir J* 2000;**16**: 1193–201.
7. Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001;**163**:1730–54.
8. Farr BM, Sloman AJ, Fisch MJ. Predicting death in patients hospitalized for community-acquired pneumonia. *Ann Intern Med* 1991;**115**:428–36.
9. Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA* 1997;**278**:2080–4.
10. Lim WS, MacFarlane JT, Boswell TC, et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. *Thorax* 2001;**56**:296–301.
11. Fine MJ, Smith MA, Carson CA, et al. Prognosis and outcomes of patients with community-acquired pneumonia, a meta-analysis. *JAMA* 1996;**275**:134–41.
12. Doern GV, Pfaller MA, Kugler K, et al. Prevalence of antimicrobial resistance among respiratory tract isolates of *Streptococcus pneumoniae* in North America: 1997 results from the sentry antimicrobial surveillance program. *Clin Infect Dis* 1998;**27**:764–70.
13. Thornsberry C, Ogilvie P, Kahn J, et al. Surveillance of antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the United States in 1996–1997 respiratory season. *Diagn Microbiol Infect Dis* 1997;**29**:249–57.
14. Doern GV, Brueggemann AB, Pierce G, et al. Antibiotic resistance among clinical isolates of *Haemophilus influenzae* in the United States in 1994 and 1995 and detection of beta-lactamase positive strains resistant to amoxicillin-clavulanate: results of a national multicenter study. *Antimicrob Agents Chemother* 1997;**41**:292–7.
15. Inoue M. Longitudinal surveillance of antibiotic resistance among clinical isolates of community-acquired respiratory tract pathogens collected in Asia in 1999/2000. ICAAC 2001, Chicago, IL (Abstract No. C2-684).
16. Felmingham D, Reinert RR. Prevalence of antibiotic resistance among European respiratory tract pathogens (1999/2000). ICAAC 2001, Chicago, IL (Abstract No. C2-685).
17. British Thoracic Society. Guidelines for the management of community-acquired pneumonia in adults admitted to hospital. Br J Hosp Med 1993; 49: 346–50.
18. Omidvari K, De Boisblanc BP, Karam G, et al. Early transition to oral antibiotic therapy for community-acquired pneumonia: duration of therapy, clinical outcomes, and cost analysis. *Respir Med* 1998;**92**: 1032–9.
19. File TM, Segreti J, Dunbar L, et al. A multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. *Antimicrob Agents Chemother* 1997;**41**:1965–72.
20. Ramirez JA, Vargas S, Ritter GW, et al. Early switch from intravenous to oral antibiotics and early hospital discharge. *Arch Intern Med* 1999;**159**:2449–54.
21. Halm EA, Fine MJ, Marrie TJ, et al. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. *JAMA* 1998;**279**: 1452–7.

22. Hitt CM, Nightingale CH, Quintiliani R, et al. Streamlining antimicrobial therapy for lower respiratory tract infection. *Clin Infect Dis* 1997;**24**(Suppl 2):S231.
23. Brueggemann AB, Kugler KC, Doern GV. In vitro activity of BAY 12-8039, a novel 8-methoxyquinolone, compared to activities of six fluoroquinolones against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. *Antimicrob Agents Chemother* 1997;**41**:1594–7.
24. Jones ME, Staples AM, Critchley I, et al. Benchmarking the in vitro activities of moxifloxacin and comparator agents against recent respiratory isolates from 377 medical centers throughout the United States. *Antimicrob Agents Chemother* 2000;**44**:2645–52.
25. Bayer Corporation. Avelox® PO/IV (moxifloxacin HCL) package insert. West Haven, CT, 2003.
26. Niederman MS, Bass JB, Campbell GD, et al. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. *Am Rev Respir Dis* 1993;**148**:1418–26.
27. Ramirez JA, Srinath L, Ahkee S, et al. Early switch from intravenous to oral cephalosporins in the treatment of hospitalized patients with community-acquired pneumonia. *Arch Intern Med* 1995;**155**:1273–6.
28. Finch R, Schurman D, Collins O, et al. Randomized controlled trial of sequential intravenous (i.v.) and oral moxifloxacin compared with sequential i.v. and oral co-amoxiclav with or without clarithromycin in patients with community-acquired pneumonia requiring initial parenteral therapy. *Antimicrob Agents and Chemother* 2002;**46**(6): 1746–54.